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## **Cetuximab induced aseptic meningitis**

Ulrich, A ; Weiler, S ; Weller, M ; Rordorf, T ; Tarnutzer, A A

**Abstract:** We report a 67-year-old man with recurrent advanced oropharyngeal squamous cell carcinoma who developed aseptic meningitis, with first symptoms arising approximately 9 hours after the first administration of cetuximab, and review the literature to identify key signs and symptoms of this condition. Cetuximab is a monoclonal antibody targeting the epidermal growth factor receptor which has been rarely associated with aseptic meningitis. Besides the case description, a MEDLINE search was performed. In five patients identified in the literature and our patient, the leading signs and symptoms included headache, neck stiffness and high fever developing within a few hours of the first cetuximab administration. Cerebrospinal fluid (CSF) analysis revealed severe pleocytosis (range: 528-2300/ l) with dominance of neutrophils ( 87%). Clinical recovery within 1-2 weeks was accompanied by normalization of CSF cell count within 4-7 days. Re-challenge with cetuximab at a reduced dose caused recurrent aseptic meningitis in one of three patients. In summary, aseptic meningitis is a rare complication after first cetuximab exposure that the clinician should be aware of. CSF analysis is the key to diagnosis and recovery is usually complete within days to weeks after withdrawal of the drug. Re-challenge may be considered but bears the risk of recurrence.

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## **Cetuximab induced aseptic meningitis - case report and review of the literature**

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Adverse drug reaction, aseptic meningitis, cetuximab, squamous cell carcinoma

## **Abstract**

Cetuximab is a monoclonal antibody targeting the epidermal growth factor receptor (EGFR), which has been rarely associated with aseptic meningitis. We report a case of aseptic meningitis with first symptoms about 9 hours after the first administration of cetuximab in a 67-year-old male with recurrent advanced oropharyngeal squamous cell carcinoma and review the literature to identify key signs and symptoms of this condition. Besides the case description a MEDLINE search was performed. In five patients identified in the literature and the patient presented here the leading signs and symptoms included headache, neck stiffness and high fever developing within few hours after first cetuximab administration. Cerebrospinal fluid (CSF) analysis revealed severe pleocytosis (range = 528-2300/ $\mu$ l) with dominance of neutrophils ( $\geq 87\%$ ). Clinical recovery within 1-2 weeks was accompanied by normalization of CSF cell count within 4 to 7 days. Re-challenge with cetuximab at a reduced dose caused recurrent aseptic meningitis in one of three patients. In summary, aseptic meningitis is a rare complication after first cetuximab exposure the clinician should be aware of. CSF analysis is the key and usually recovery is complete within days to weeks after withdrawal of the drug. Re-challenge may be considered but bears the risk of recurrence.

Cetuximab, a chimeric monoclonal antibody against the epidermal growth factor receptor (EGFR) has demonstrated activity as a single agent and in combination with chemotherapy or radiation in the treatment of metastatic or recurrent squamous cell cancer of head and neck, and in colorectal adenocarcinoma [1, 2]. Aseptic meningitis has been observed as a rare complication of cetuximab administration.

Here we report aseptic meningitis after the first cetuximab administration ( $400\text{mg/m}^2$ ) in a 67-year-old male treated for advanced oropharyngeal squamous cell carcinoma progressing on prior platinum-based treatment. Approximately nine hours after cetuximab infusion the patient complained of headache, showing neck stiffness, fever ( $39.2^\circ\text{C}$ ) and psychomotor slowing. Cranial computed tomography revealed leucencephalopathy, but no other abnormalities. Cerebrospinal fluid (CSF) analysis (see Table 1) demonstrated an elevated cell count ( $1413/\mu\text{l}$ ; normal range:  $0\text{--}4/\mu\text{l}$ ) with 92% neutrophil granulocytes, 8% macrophages and no cancer cells. Gram staining was negative. CSF protein was elevated ( $1.786\text{ g/l}$ ; normal range  $0.2\text{--}0.4\text{ g/l}$ ), while glucose was normal ( $3.5\text{ mmol/l}$ , normal range  $2.7\text{ to }4.2\text{ mmol/l}$ ) and lactate was only slightly elevated ( $3.0\text{ mmol/l}$ , normal range  $1.7\text{ to }2.6\text{ mmol/l}$ ). Antibiotic and antiviral treatment was initiated with ceftazidim, vancomycin, amoxicillin and aciclovir plus dexamethasone. Treatment was stopped a few days later when PCR of neurotropic viruses (herpes simplex virus 1&2, varicella-zoster virus, cytomegalovirus, Epstein-Barr virus), bacterial cultures/staining and fungal staining returned negative. We therefore interpreted the patient's condition as aseptic meningitis related to cetuximab. The patient gradually improved over the following days. Repeat CSF analysis eight days after admission (see Table 1) showed normalization of cell count ( $1/\mu\text{l}$ ); while CSF protein was still elevated ( $0.682\text{ g/l}$ ). CSF glucose ( $4.0\text{ mmol/l}$ ) and lactate ( $1.5\text{ mmol/l}$ ) levels were normal and oligoclonal bands were negative. Another seven days later, CSF protein level had normalized, too ( $0.359\text{ g/l}$ ). The patient was discharged for rehabilitation four weeks after cetuximab treatment. Re-challenge with rituximab was not considered because of the reduced general condition due to tumor

progression and comorbidities (end stage renal failure). The patient died six weeks later probably related to cardiac arrhythmias.

A MEDLINE-search ('cetuximab AND aseptic meningitis') identified three publications reporting on five patients (Table 2) [3-5]. Dose ( $400\text{mg/m}^2$ ) and application (rate=2h; first administration) of cetuximab were identical and symptom-onset was delayed by a few hours. Clinical presentation was similar with severe headaches, high fever and neck stiffness. CSF analysis revealed pleocytosis (range=528-2300/ $\mu\text{l}$ ) with a dominance of neutrophil granulocytes ( $\geq 87\%$ ). All patients recovered, usually within one week, as also reflected by normalization of CSF cell count. While re-challenge with cetuximab (with dose reduced to  $250\text{mg/m}^2$ ) was feasible in two cases [5], recurrent aseptic meningitis was reported in another case [4].

A search in the WHO Global Database of Individual Case Safety Reports (ICSR) ('cetuximab AND aseptic meningitis') identified 21 cases (2005-2014) from a total of 15.456 ICSRs involving cetuximab, but no further information about clinical presentation, recovery or CSF results was available.

Aseptic meningitis must be recognized as a rare and self-limiting adverse event that usually occurs within few hours after the first cetuximab administration. The combination of sudden headache, neck stiffness and high fever should prompt immediate CSF analysis including a broad search for bacterial, fungal or viral infections. Whereas the initial CSF inflammatory response is severe, a remarkably fast normalization of the CSF cell count accompanied by a rapid reduction of CSF protein is characteristic. Based on five published cases and 21 cases in the ICSR database, aseptic meningitis might be a very rare event after cetuximab treatment. The crossing of IgG over the blood-brain barrier might play a role in its pathogenesis [4]. Drug-induced meningitis as a diagnosis of exclusion was reported with other therapeutic

antibodies too, most frequently with the application of intravenous immunoglobulins (IVIGs) [6, 7]. Slowing the infusion rate, reducing the dose and premedication with steroids was proposed [5] in analogy to recommendations for the application of IVIGs [6, 7]. This approach was associated with lack of recurrence only in two of three cases.

In summary, because of its characteristic clinical presentation, tight temporal association to the first cetuximab application and negative CSF cultures/serologies, the clinician can identify this rare and self-limiting adverse event reliably. While antibiotic and virostatic treatment is initially advised, symptomatic treatment is sufficient as soon as CSF cultures/serologies return negative. Prognosis is usually good with complete recovery within 1-2 weeks. The decision for re-challenge with cetuximab must be made on an individual basis, but bears the risk of recurrence.

## **Tables**

<b>Table 1:</b> CSF– evolution over time after application of cetuximab (=day 1)			
<i>parameter</i>	<i>day 1</i>	<i>day 8</i>	<i>day 15</i>
cell count (normal range: 0-4/ $\mu$ l)	1413	1	1
neutrophils (%)	92%	NA	NA
CSF protein (normal range: 0.2-0.4g/l)	1.786	0.682	0.359
glucose (normal range 2.7 to 4.2 mmol/l)	3.5	4.0	2.8
lactate (normal range 1.7 to 2.6 mmol/l)	3.0	1.5	1.7
PCR (cytomegalovirus, Epstein-Barr virus, herpes simplex virus 1&2, varicella-zoster virus)	negative	NA	NA
microbiology (Cytosin- and periodic-acid-Schiff-staining)	negative	NA	NA
oligoclonal bands	NA	negative	NA
cancer cells	negative	NA	NA

Abbreviations: CSF=cerebrospinal fluid; NA=not available; PCR=polymerase chain reaction

<b>Table 2:</b> characteristics of the five reported cases in the literature * and comparison with the presented case								
<i>study</i>	<i>case #, age, gender</i>	<i>type of cancer / indication for cetuximab</i>	<i>cetuximab dose, premedication</i>	<i>symptoms and signs (onset), imaging</i>	<i>initial CSF analysis (cell count, protein level)</i>	<i>follow-up CSF analysis</i>	<i>treatment, recovery</i>	<i>re-challenge</i>
Emani & Zaiden 2012 [4]	1, 54y, f	squamous maxillary cancer (stage IVb)	400mg/m <sup>2</sup> (first application), yes (diphenhydramine 50mg i.v.)	frontal headache, neck discomfort, 39.9°C fever (few hours after infusion), brain CT (normal)	1025/μl with 92% neutrophils, protein 1.65g/l, normal glucose level, neg. bacterial culture, PCRs (HSV) neg.	NA	empirical antibiotic tx. Resolution of sx, no complications.	positive re-challenge after 4 weeks (250mg/m <sup>2</sup> ), recurrent CSF pleocytosis (715/μl, 93% neutrophils), protein 1.22g/l, premedication: diphenhydramine, no steroids †
Feinstein et al. 2009 [5]	2, 45y, m	recurrent laryngeal squamous cell carcinoma	400mg/m <sup>2</sup> (first application, duration 2h), yes (diphenhydramine 50mg i.v.)	frontal headache, 38.9°C fever (few hours after infusion), brain imaging NR	2300/μl with 98% neutrophils, protein 1.04g/l, normal glucose level, neg. cultures	“resolution of neutrophilic pleocytosis”, normal protein levels (day 4)	empirical antibiotic tx, aciclovir. No information about recovery	negative re-challenge after 1 week (250mg/m <sup>2</sup> , premedication: dexamethasone, diphenhydramine) without adverse events
	3, 42y, m	locally advanced squamous cell carcinoma of right tonsil	400mg/m <sup>2</sup> (first application, duration 2h), yes (diphenhydramine 50mg i.v.)	severe frontal headache, 39.4°C fever, neck stiffness, photophobia (≈8h after infusion), brain imaging NR	2267/μl with 90% neutrophils, protein 1.46g/l, normal glucose level, neg. cultures	“no white blood cells”, elevated but improved protein (69mg/dl)	empirical antibiotic tx, acyclovir, dexamethasone. Recovery from meningeal sx after 12 days	negative re-challenge after 2 weeks (250mg/m <sup>2</sup> , premedication: dexamethasone, diphenhydramine, famotidine) without adverse events
Nagovski y et al. 2010 [3]	4, 78y, f	NSCLC (stage IIIA)	400mg/m <sup>2</sup> (first application, duration NR), NR	severe headache, nausea, vomiting, neck stiffness (few hours after infusion), brain CT (normal)	528/μl with 87% neutrophils ‡, “modestly elevated protein”, normal glucose levels	NA	empirical antibiotic tx (stopped after infection was ruled out). Recovery w/o neurological sequelae.	NR
	5, 59y, m	metastatic NSCLC	400mg/m <sup>2</sup> (first application, duration NR), NR	acute encephalopathy (few hours after infusion), brain CT and MRI (normal)	cell count and fraction of neutrophils NA §, protein 1.16g/l, glucose 2.8mmol/l, neg. cultures	NA	empirical antibiotic tx (stopped after infection was ruled out). Recovery “within several days”	NR
Present case	6, 67y, m	recurrent advanced oropharyngeal squamous cell carcinoma	400mg/m <sup>2</sup> (first application, duration 2h), yes (clemastine 2mg p.o.)	headache, mutism, hypertension, neck stiffness, 39.2°C fever (≈9h after infusion), brain CT and MRI (non-diagnostic)	1413/μl (normal range 0-4/μl) with 92% neutrophils, protein 1.79g/l (normal range <0.4), normal glucose level (3.5mmol/l), neg. cultures / serologies	1/μl, protein 0.68g/l, normal glucose level (4.0 mmol/l)	empirical antibiotic tx, dexamethasone (stopped after infection was ruled out). Myoclonic jerks and NCSE after 3 days. Recovery within 14 days.	the patient and his family decided against re-challenge of cetuximab. The patient was transferred to the hospice where he died 4 weeks later.



\* We identified one additional case report with aseptic meningitis (dosage 100mg/m<sup>2</sup>) from a phase 1 study [8]. With no further details available on this patient we did not include it in the table.

† Treatment with cetuximab was continued after the positive re-challenge, but no further adverse events occurred on exposures 3 and following.

‡ Based on the reported number of segmented polymorphonuclear leukocytes (459/μl), that made up 87% of all cells, a total CSF cell count of 528/μl was calculated.

§ Nagovski and colleagues stated: „CSF evaluation showed 214 nucleated cells, 15 red blood cells, 81 segmented cells, and seven lymphocytes“ without providing further details such as total CSF cell count and whether these numbers were per μl. Contacting the authors for clarification of the CSF cell count in this patient remained unsuccessful.

|| The further treatment options were limited due to the failure of carboplatin and paclitaxel as well as preexisting end-stage renal disease and dialysis three times a week. The administration of methotrexate has been reported in patients with end stage renal disease but daily dialysis was necessary. In palliative situation and short life expectancy we did not consider this an option. Due to difficulties swallowing, the treatment with capecitabine was not possible and continuous infusion of 5-fluorouracil during 5 days could not have been administrated because of dialysis.

Abbreviations: CSF=cerebrospinal fluid; CT=computed tomography; HSV=herpes simplex virus; MRI=magnetic resonance imaging; NA=not available; NCSE=non-convulsive status epilepticus; NR=not reported; NSCLC=non-small cell lung cancer; PCR=polymerase chain reaction.

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